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CAROTENOIDS, VITAMIN A AND RISK OF ADENOMATOUS POLYP RECURRENCE IN THE POLYP PREVENTION TRIAL

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One trial reported beta-carotene supplementation was protective of adenomatous polyp recurrence in nonsmokers. We now examine the relation of serum and dietary carotenoids and vitamin A to adenomatous polyp recurrence in a subcohort of 834 participants in a low fat, high fiber, high fruit and vegetable dietary intervention, the Polyp Prevention Trial. Multivariate odds ratio (OR) and 95% confidence intervals (CI) of polyp recurrence were obtained using baseline or the average (first 3 years of the trial) carotenoid and vitamin A values after adjustment for covariates. Compared to the lowest quartile of baseline alpha-carotene concentrations, the OR of multiple polyp recurrence for the highest quartile was 0.55 (95% CI = 0.30–0.99) and the OR of right-sided recurrence was 0.60 (95% CI = 0.37–0.95). Baseline dietary intakes of alpha-carotene and vitamin A from food with/without supplements were inversely associated with any recurrence ($p_{\text{for linear trend}} = 0.03$- alpha-carotene; $p = 0.004$ and $p = 0.007$ -intakes of vitamin A). Compared to the lowest quartile of averaged beta-carotene concentrations, the OR of multiple adenomas for the highest quartile was 0.40 (95% CI = 0.22–0.75) with an inverse trend ($p = 0.02$). The risk was inversely related to averaged: alpha-carotene concentrations and right-sided polyps; alpha-carotene intake and recurrence of any, multiple and right-sided polyps; beta-carotene intake and multiple adenoma recurrence; vitamin A from food (with supplements) and each adverse endpoint. Thus, alpha-carotene and vitamin A may protect against recurrence in nonsmokers and nondrinkers or be indicative of compliance or another healthy lifestyle factor that reduces risk.

Key words: *carotenoids; vitamin A; adenomatous polyps; epidemiology*

Carotenoids are fat-soluble pigments found primarily in fruits and vegetables. Besides the well-known provitamin A activity of hydrocarbon carotenoids, numerous mechanisms have been postulated for carotenoid effects on carcinogenesis including inhibition of growth and induction of differentiation of cancer cells by modulating the expression of cell cycle regulatory proteins, modulation of the IGF-1/IGFPB-3 system, enhancement of immune function, increased gap junction intracellular communication, modulation of redox signaling and prevention of oxidative DNA damage and modulation of carcinogen metabolizing enzymes.[1] Consumption of carotenoid-rich fruits and vegetables has been associated with a reduction in risk of colorectal, lung, ovarian and other cancers.[2–5] However, few epidemiologic studies have examined individual carotenoid or vitamin A intake or serum concentrations and risk of colorectal cancer or adenomatous polyps, which are precursors to colorectal cancer. In a large beta-carotene supplementation trial of adenoma recurrence, similar in design to the Polyp Prevention Trial (PPT), participants in the beta-carotene supplemented group (20 mg/day) and placebo group experienced a similar rate of adenoma recurrence by intent to treat analysis.[6] In a subsequent analysis, stratified by smoking and drinking status, a significant protective effect from beta-carotene supplementation was observed in nonsmoking and nondrinking individuals.[7]

Colorectal cancer is the third leading cancer in men and women in the U.S., resulting in an estimated 56,600 deaths in the year 2002.[8] While not all adenomas develop into cancer, it is believed that at least 95% of all colorectal cancers are derived from adenomatous polyps. The prevalence of colorectal adenomas in the U.S. ranges from 35–60%,[9] and recurrence of adenomas has been estimated at 10% or more annually.[10] Factors associated with recurrence of these lesions, including adenoma and patient characteristics, are not fully understood; however, a number of studies have demonstrated an increased recurrence of adenomas in individuals with a history of multiple adenomas.[11,12] Thus, reducing the incidence or recurrence of any or multiple adenoma formation is a plausible means for preventing colorectal cancer. Since genetic and epidemiology data suggest differences in colorectal cancer[13]

Abbreviations: BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; GAM, generalized additive model; LRT, log likelihood ratio test; NSAIDS, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PPT, Polyp Prevention Trial.

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and adenoma[14] by location within the large bowel, we also examined the associations of carotenoids and vitamin A separately for left- and right-sided adenomas.

The Polyp Prevention Trial (PPT) was a large randomized dietary intervention designed to test the hypothesis that a high fiber, high fruit and vegetable and low fat diet reduces the risk of adenomatous polyp recurrence after 4 years of follow-up.[15] No difference in adenomatous polyp recurrence was observed in participants on the intervention arm compared to those consuming their normal diet.[16] The purpose of this investigation was to examine the association between serum concentrations and dietary intake of 5 major carotenoids and vitamin A collected at baseline and then years 1–3 of the intervention study with endpoints in year 4 of any, multiple and right- or left-sided adenomatous polyp recurrence in a random subcohort of the PPT. Because half of the subjects were instructed to consume a high fruit and vegetable diet, we examined the associations for intervention and control groups separately, as well as for all subjects combined.

MATERIAL AND METHODS

Subjects

The PPT design and methods have been described in detail elsewhere.[15,17] Briefly, subjects, who were $\geq$ 35 years and who had one or more histologically confirmed colorectal adenoma removed during colonoscopy within 6 months prior to randomization were recruited into the study through endoscopist referrals or review of medical records at 8 clinical centers in the U.S. Exclusions from trial eligibility included prior history of colorectal cancer, surgical resection of adenomas, bowel resection, the polyposis syndrome or inflammatory bowel disease; $>$ 150% of ideal body weight; use of lipid-lowering drugs and medical conditions or dietary practices that would substantially limit compliance with the intervention. All subjects provided written informed consent, and a total of 1,905 subjects completed the trial. Blood was analyzed for lipids, vitamin A and carotenoids to monitor dietary compliance in 44% (n=834) who were selected to reflect the proportionate distribution of gender in each of 8 clinical centers. Half of these subjects (n=419) were enrolled in the intervention arm of the trial and half (n=415) were in the control arm on their usual diet.

Study design

At 1 and 4 years after randomization, colonoscopy was performed on all subjects. The purpose of the 1-year colonoscopy was to remove any adenomas missed at baseline. Two central pathologists who were blind to the subjects' group assignments determined the histologic features and degree of atypia of all adenomas. The endoscopists reported the size, number and location of all adenomas. Endpoint adenoma recurrence was defined as any adenomatous polyp discovered after the 1-year colonoscopy and identified 3 years later on average at the 4-year colonoscopy.

All subjects provided a venous blood sample after an overnight fast at baseline and annually for 4 years of follow-up (total of up to 5 samples per subject). Concentrations of 5 different carotenoids (alpha-carotene, beta-carotene, lutein/zeaxanthin, beta-cryptoxanthin and lycopene) and vitamin A were measured using High Performance Liquid Chromatography (HPLC) in serum samples.[18] The coefficients of variation for 109 blinded quality control samples were 6.4% for beta-carotene, 6.9% for alpha-carotene, 8.2% for lutein/zeaxanthin, 7.3% for lycopene, and 12.4% for beta-cryptoxanthin and 3.2% for vitamin A. A modified Block/NCI, 101-item, food frequency questionnaire (FFQ) was administered by interviewers at baseline and annually for 4 years to collect dietary intake in all subjects. Values from the 1998 USDA/NCI carotenoid food composition database were used to estimate carotenoid intake.[19,20] Subjects completed a lifestyle questionnaire at each time point. Carotenoid and vitamin A values in blood and reported from diet that were collected near the final colonoscopy, typically at the end of 4 years, were excluded from data analysis because they may have been influenced by disease status.

Statistics

The statistical analyses involved 3 phases and treated the subcohort as an observational prospective cohort. In the first phase, Student's t-tests were calculated to compare mean serum and dietary carotenoids and vitamin A at baseline as well as demographic characteristics in subjects with any (or multiple, right- or left-sided) adenomatous polyp recurrence compared to subjects without recurrence.

In Phase II, odds ratios (OR) were computed from multiple logistic regression models of the following endpoints: any adenoma recurrence, multiple adenoma recurrence, any right- or left-sided recurrence [including an adenoma recurrence on the right (or left) side only plus a recurrence on both the right-side and the left-side]. Adverse endpoints (with numbers indicated in tables) were compared with 510/511 nonrecurrences at baseline (for dietary and serum parameters, respectively) and with 485 nonrecurrences during years 1–3 of the PPT. Major independent variables were (log-transformed) baseline and the average over years 1 to 3 of serum and dietary intakes of carotenoids and vitamin A. Analysis of baseline data before randomization from data collected during the nonblinded dietary intervention provides the opportunity to test for separate effects from the dietary intervention. The averaged serum and dietary data were estimated from at least 2 blood draws or FFQs completed over the three year period. Use of 2 or more estimates had the advantage of reducing intraindividual variability in the blood and dietary parameters that reflect trial period exposures but the disadvantage of reducing the sample sizes for analysis from baseline to the intervention years.

Serum and dietary intakes were categorized in quartiles, ranging from 1 being the lowest (referent) to 4 being the highest levels of intake and serum concentrations. Because the data were collected prospectively, the quartile cut-points were determined by the distribution of serum and dietary carotenoids and vitamin A in the total subcohort. Each of the 5 individual carotenoids plus the total (the sum of all 5 carotenoids) was analyzed in a separate model because of high inter-correlations between carotenoids. Specifically, the range in Spearman rank correlation coefficients of each carotenoid with the sum total of all 5 carotenoids at baseline and over the 3-year trial period, respectively, were 0.71 and 0.80 for alpha-carotene, 0.84 and 0.87 for beta-carotene, 0.70 and 0.72 for beta-cyptoxanthin; 0.71 and 0.69 for lutein/zeaxanthin and 0.55 and 0.48 for lycopene. Spearman rank correlation coefficients of an individual carotenoid and the total of the 4 remaining carotenoids were slightly lower.

The test for linear trend was calculated by replacing the raw values with the scores for the median of each quartile for a carotenoid or vitamin A and then treating the scores as a continuous variable in the logistic regression model. The log likelihood ratio test (LRT) was performed to assess whether the model within quartiles of carotenoids or vitamin A fit better than the model without the quartiles. As the p-values from the LRT method were similar to those from the trend test, only the p-values for trend are presented in the tables.

Multiple logistic regression models of all endpoints were recomputed for the intervention and control groups, separately, as well as by gender for the entire subcohort. Since the test for interaction of the baseline or averaged serum carotenoids and treatment group were not statistically significant, results are presented in tabular form for the entire subcohort. However, when differences in the intervention or control group appear consistently over the trial, these findings are highlighted. Individuals with adenomatous polyps at the colonoscopy in the first year of the PPT were excluded from the analysis to remove any influence of potentially missed polyps at baseline. No differences were observed with their removal; thus all participants were retained in the models.

Potential confounding effects or effect modification was examined for age, gender, intervention group assignment, gender*group interaction (there was a significant interaction between gender and intervention group in the original study[16]), date of blood draw (reflecting seasonality of consumption of carotenoid-rich foods), center location (which may be an indictor of availability of carotenoid-rich fruits and vegetables, and thus intake and serum levels), race, education level, body mass index (BMI), alcohol intake, smoking, use of hormone replacement therapy (in women), serum cholesterol, nonsteroidal anti-inflammatory drug (NSAIDS) use at baseline, physical activity, multiple adenomas at baseline and intake of energy, folate and calcium. Effect modification was analyzed by 2 methods: 1) stratifying by categories of the covariate and 2) entering the crossproduct of the covariate and the carotenoid or vitamin A variable (the interaction term) into the logistic regression model. All analyses adjusted for age, gender, NSAIDS use, intervention group and the interaction between gender and intervention group because these covariates were identified as confounding factors in preliminary models.

In Phase III, significant food predictors of average serum alpha-carotene concentrations were derived from linear regression analysis described previously.[21] Also, the percent contribution of each carotenoid-containing fruit and vegetable to the total dietary intake of alpha carotene was calculated using FFQ reported data. All *p*-values correspond to 2-sided test of the hypothesis, with $p < 0.05$ considered statistically significant. SAS statistical software version 8.2 was used for all analyses (SAS Institute, Cary, NC).

RESULTS

Thirty-nine percent of subjects in this subcohort experienced a recurrence of any adenomatous polyp at the end of the study period, similar to the overall PPT population[16] (Table I). Approximately 17% of the subcohort and overall PPT population experienced multiple adenoma recurrence. Additionally, 18% had only right-side adenomas and 12% only left-side adenoma recurrence, with another 8% of individuals diagnosed with recurrences on both the left and right side. Similar to the participants in the overall PPT, the average age of this subcohort was 61 years, and 67% were male. Most were nonsmokers, and more than half (58.4%) reported regular alcohol consumption. Only 17% consumed more than one drink/day. The average ages of subjects who experienced any (or multiple or a right- or left-sided) adenoma recurrence were significantly older than those who did not experience a recurrence, and a higher proportion of men experienced an adverse endpoint compared to the percentage without a recurrence. A higher proportion of subjects who experienced multiple adenomatous polyp recurrence were Caucasian than the proportion without a recurrence. Individuals who experienced a left-sided adenoma recurrence had a higher mean BMI compared to those without recurrence, and a higher proportion who experienced a right-sided adenoma recurrence had a high school education or less compared to those who experienced no recurrence. No significant demographic and lifestyle differences were observed between participants in the intervention and those on their usual diet (control group).

Baseline serum concentrations of alpha-carotene and beta-carotene were significantly lower in participants who experienced any or multiple or right-sided adenoma recurrence than in those without a recurrence (Table II*a*). Baseline total dietary carotenoid intake was significantly lower in participants who experienced any or multiple adenoma recurrence than in the nonrecurrences. The average of years 1–3 of serum concentrations of alpha-carotene, beta-carotene, lycopene and total carotenoids were significantly lower in patients who experienced multiple adenoma recurrence compared to those without a recurrence (Table II*b*). Also, average serum alpha-carotene and beta-carotene concentrations were lower in patients who had any or a right- or left-sided recurrence than in those without a recurrence. Compared to the nonrecurrences, dietary intakes that were averaged over years 1–3 were significantly lower for lycopene among subjects who had a multiple or left-sided recurrence, for total carotenoids among subjects who had any or right- or left-sided recurrence and lower for vitamin A intakes from food alone or with supplements among subjects who had a right-sided or any recurrence, respectively.

Multiple logistic regression models of baseline comparisons

A borderline nonsignificant inverse association between serum alpha-carotene concentrations at baseline and any recurrence was observed ($p_{\text{for linear trend}} = 0.06$) (Table III*a*). Compared to the lowest quartile of serum alpha-carotene, the highest quartile had 45% lower odds of multiple adenoma recurrence and 40% lower odds of right-sided adenoma recurrence, with a significant inverse trend. Although the test for interaction between group and baseline serum levels was not significant, the highest quartile of serum alpha-carotene at baseline in the intervention group experienced a significant reduction in any recurrence (O.R. = 0.47, 95% CI = 0.26–0.87), in multiple adenoma recurrence (O.R. = 0.37, 95% CI = 0.16–0.87), and in right-sided adenoma recurrence (O.R. = 0.42, 95% CI = 0.22–0.81) (data not shown). The inverse relation of baseline serum alpha-carotene and the OR of each adverse endpoint mentioned above was significant, with a $p_{\text{for linear trend}} = 0.009$ for any recurrence, $p = 0.03$ for multiple adenoma and $p = 0.006$ for right-sided adenoma recurrence. No appreciable effects were observed in the control group at baseline.

Baseline dietary intake of alpha-carotene was inversely related to any adenoma recurrence ($p = 0.03$) in the entire cohort (Table III*b*). Baseline dietary intakes of vitamin A from food alone and total vitamin A intake (from food plus supplements) were inversely related to the recurrence of any, multiple, and right-sided adenomas, with $p_{\text{for linear trend}} = 0.004$, $p_{\text{for linear trend}} = 0.001$ and $p_{\text{for linear trend}} = 0.006$ for each endpoint, respectively, related to vitamin A food sources and $p_{\text{for linear trend}} = 0.007$, $p_{\text{for linear trend}} = 0.01$ and $p_{\text{for linear trend}} = 0.01$ for each endpoint, respectively, related to total vitamin A intake. Compared to the first quartile, individuals in the third and fourth quartiles of intake of vitamin A

TABLE I – DEMOGRAPHIC AND OTHER CHARACTERISTIC OF THE STUDY POPULATION AT BASELINE: PPT

Characteristics	All subjects ($n = 834$)	No recurrence ($n = 511$)	Any adenoma recurrence ($n = 323$)	Multiple adenoma recurrence ($n = 147$)	Right-sided adenoma recurrence ($n = 217$)	Left-sided adenoma recurrence ($n = 164$)
Age, years	60.7 ± 9.9	59.1 ± 10.1	63.2 ± 8.9[1]	65.7 ± 8.6[1]	64.2 ± 8.8[1]	62.7 ± 9.3[1]
Gender, % male	67.3	62.4	74.9[1]	76.9[1]	74.7[2]	73.2[2]
BMI, kg/m^2	27.5 ± 3.9	27.3 ± 4.0	27.8 ± 3.7	28.0 ± 3.5	27.6 ± 3.7	28.1 ± 3.6[2]
Current smokers, %	12.2	11.9	12.7	10.2	12.0	14.0
Current drinkers, %	58.4	58.3	58.5	53.7	58.1	58.5
Alcohol, grams/day	7.3 ± 12.4	6.6 ± 11.4	8.3 ± 13.9	7.8 ± 14.4	8.0 ± 13.6	7.8 ± 12.8
Education, % high school or less	22.5	20.7	25.4	27.2	28.6[2]	25.6
Race, % Caucasian	88.8	89.2	88.2	93.9[2]	90.3	88.4
Family history of cancer, %	24.8	24.9	24.8	27.2	26.3	27.4

[1]Comparison group: no adenoma recurrence; $p \leq 0.01$.– [2]Comparison group: no adenoma recurrence; $p \leq 0.05$.

TABLE IIA – MEAN AND STANDARD DEVIATIONS OF SERUM CONCENTRATIONS OF AND DIETARY INTAKES OF CAROTENOIDS AND VITAMIN A AT BASELINE BY ADENOMA RECURRENCE STATUS: PPT

Characteristics	All subjects baseline	Non-recurrence	Any adenoma recurrence	Multiple adenoma recurrence	Right-sided adenoma	Left-sided adenoma
Mean serum (ug/dl)	(N = 834)	(N = 511)	(N = 323)	(N = 147)	(N = 217)	(N = 166)
Alpha-carotene	6.8 ± 6.3	7.3 ± 7.3	6.0 ± 4.4[1]	5.7 ± 3.9[1]	5.6 ± 3.4[1]	6.3 ± 5.1
Beta-carotene	25.5 ± 21.8	26.8 ± 23.9	23.5 ± 18.0[3]	22.4 ± 17.9[3]	23.4 ± 19.2[3]	23.4 ± 18.2
Beta-cryptoxanthin	11.2 ± 7.6	11.1 ± 7.2	11.2 ± 8.2	10.7 ± 9.0	11.2 ± 9.0	11.0 ± 6.4
Lutein	25.4 ± 11.9	25.7 ± 12.4	24.8 ± 11.2	24. ± 10.5	24.6 ± 10.8	24.6 ± 11.5
Lycopene	23.8 ± 10.9	23.9 ± 11.0	23.7 ± 10.6	22.6 ± 10.6	23.5 ± 10.6	22.8 ± 10.8
Total carotenoids	92.7 ± 40.9	94.9 ± 43.0	89.2 ± 37.0	85.9 ± 35.2	88.1 ± 36.8	88.2 ± 37.3
Retinol	64.3 ± 14.9	63.5 ± 14.9	65.4 ± 14.7	66.3 ± 15.8	65.1 ± 13.1	65.6 ± 16.1
Mean dietary (mg/d)	(N = 834)	(N = 511)	(N = 323)	(N = 147)	(N = 217)	(N = 166)
Alpha-carotene	0.45 ± 0.40	0.47 ± 0.43	0.42 ± 0.35	0.44 ± 0.32	0.43 ± 0.36	0.43 ± 0.32
Beta-carotene	2.85 ± 1.82	2.90 ± 1.90	2.76 ± 1.70	2.76 ± 1.63	2.78 ± 1.64	2.81 ± 1.65
Cryptoxanthin	0.04 ± 0.04	0.04 ± 0.04	0.04 ± 0.04	0.04 ± 0.04	0.04 ± 0.04	0.04 ± 0.03
Lutein	2.51 ± 2.02	2.49 ± 1.99	2.54 ± 2.06	2.54 ± 2.03	2.51 ± 1.72	2.64 ± 2.27
Lycopene	2.56 ± 1.86	2.55 ± 1.74	2.57 ± 2.04	2.66 ± 2.15	2.54 ± 1.97	2.68 ± 2.29
Total carotenoids	8.41 ± 4.73	8.45 ± 4.68	8.33 ± 4.81[3]	8.43 ± 4.92[2]	8.31 ± 4.42	8.61 ± 5.09
Vitamin A, food alone	1.45 ± 0.72	1.48 ± 0.74	1.41 ± 0.69	1.40 ± 0.71	1.48 ± 0.74	1.43 ± 0.66
Vitamin A, food + supplements	2.24 ± 1.39	2.30 ± 1.45	2.15 ± 1.28	2.11 ± 1.23	2.12 ± 1.27	2.19 ± 1.21

[1]Comparison group: no adenoma recurrence; $p \leq 0.001$.– [2]Comparison group: no adenoma recurrence; $p \leq 0.01$.– [3]Comparison group: no adenoma recurrence; $p \leq 0.05$.

TABLE IIB – MEAN AND STANDARD DEVIATIONS OF THE AVERAGE OF YEARS 1 TO 3 OF SERUM CONCENTRATIONS OF AND DIETARY INTAKES OF CAROTENOIDS AND VITAMIN A BY ADENOMA RECURRENCE STATUS: PPT

Serum or dietary carotenoid or vitamin A (T1–T3)	All subjects (T1–T3)	Nonrecurrence	Any adenoma recurrence	Multiple adenoma recurrence	Right-sided adenoma	Left-sided adenoma
Mean serum (ug/dl)	(N = 781)	(N = 481)	(N = 300)	(N = 135)	(N = 202)	(N = 154)
Alpha-carotene	7.1 ± 5.3	7.6 ± 6.0	6.4 ± 3.9[1]	6.1 ± 3.5[1]	6.2 ± 3.7[1]	6.3 ± 3.6[2]
Beta-carotene	29.1 ± 23.5	31.0 ± 26.6	26.1 ± 17.2[2]	24.3 ± 15.9[1]	27.1 ± 18.5[3]	24.6 ± 14.3[1]
Beta-cryptoxanthin	12.0 ± 7.4	12.1 ± 7.8	11.9 ± 6.6	12.0 ± 7.2	11.7 ± 6.1	12.0 ± 7.0
Lutein	27.4 ± 11.7	27.8 ± 11.8	26.7 ± 11.5	26.3 ± 11.5	26.7 ± 11.6	26.2 ± 11.2
Lycopene	23.5 ± 9.4	23.8 ± 9.5	23.2 ± 9.2	21.9 ± 8.8[3]	23.0 ± 8.9	22.8 ± 10.8
Total carotenoids	99.1 ± 40.9	102.2 ± 43.7	94.3 ± 35.4	90.6 ± 35.1[2]	94.6 ± 35.5	91.9 ± 33.8[2]
Retinol	66.1 ± 14.4	65.7 ± 14.7	66.8 ± 14.2	68.3 ± 15.8	66.6 ± 13.5	67.2 ± 14.8
Mean dietary (mg/d)	(N = 795)	(N = 484)	(N = 311)	(N = 139)	(N = 209)	(N = 159)
Alpha-carotene	0.57 ± 0.39	0.60 ± 0.43	0.53 ± 0.32	0.55 ± 0.36	0.53 ± 0.32	0.52 ± 0.34
Beta-carotene	3.83 ± 2.15	3.92 ± 02.23	3.69 ± 1.94	3.77 ± 2.12	3.72 ± 1.96	3.60 ± 1.99
Cryptoxanthin	0.06 ± 0.04	0.05 ± 0.04	0.06 ± 0.04	0.06 ± 0.04	0.06 ± 0.04	0.06 ± 0.04
Lutein	3.50 ± 2.38	3.53 ± 2.43	3.46 ± 2.31	3.60 ± 2.30	3.52 ± 2.42	3.27 ± 2.01
Lycopene	3.05 ± 1.88	3.12 ± 1.97	2.92 ± 1.71	2.81 ± 1.50[3]	2.94 ± 1.69	2.81 ± 1.58[3]
Total carotenoids	11.0 ± 5.62	11.22 ± 5.84	10.66 ± 5.26[2]	10.79 ± 5.35	10.76 ± 5.33[3]	10.27 ± 4.92[3]
Vitamin A, food alone	1.68 ± 0.74	1.70 ± 0.76	1.64 ± 0.71	1.65 ± 0.74	1.64 ± 0.69[2]	1.64 ± 0.71
Vitamin A, food + supplements	2.75 ± 1.44	2.84 ± 1.55	2.59 ± 1.22[3]	2.60 ± 1.26	2.54 ± 1.18	2.63 ± 1.27

[1]Comparison group: no adenoma recurrence; $p \leq 0.001$.– [2]Comparison group: no adenoma recurrence; $p \leq 0.01$.– [3]Comparison group: no adenoma recurrence; $p \leq 0.05$.

from food had lower odds of any recurrence by 48 and 50%, of multiple adenomas by 65 and 67%, and of right-sided recurrence by 51 to 54%. Similar reductions in the odds of recurrence were observed for individuals in the fourth compared to the first quartile of total vitamin A intake (from food and supplements) for all endpoints. Moreover, similar patterns in baseline alpha-carotene and vitamin A intakes appeared in the intervention, not the control, group, but the interaction between group assignment and dietary intake was not significant. No significant effects of dietary intake or serum concentrations of the carotenoids or vitamin A on left-sided adenoma recurrence were observed (data not shown).

Multiple logistic regression models of recurrence using averaged serum concentrations of and dietary intake of carotenoids and vitamin A from the first 3 years of the PPT

During the first 3 years of the dietary intervention period (T1–T3), there was an inverse association between serum concentrations of alpha-carotene and the odds of right-sided adenoma recurrence (p=0.04) (Table IV*a*). There was an inverse association between serum concentrations of beta-carotene and multiple adenoma recurrence (p=0.02), with individuals in the highest (*vs*. the lowest) quartile of serum beta-carotene experiencing a 60% lower odds of recurrence. A 48% lower odds of multiple adenoma recurrence was observed in the highest compared to the lowest quartile of the total averaged serum carotenoids. In a comparison of the intervention and control groups, a strikingly similar pattern of significant inverse associations between serum alpha-carotene concentrations and the odds of any recurrence and that of right-sided adenoma recurrence appeared in the intervention, not the control, group, yet the test for interaction was not significant (data not shown).

In the analysis of the averaged dietary intake during the first through third years of the trial, there was an inverse association between dietary intake of alpha-carotene and any recurrence (p = 0.03), multiple adenoma recurrence (p = 0.05), and right-sided adenoma recurrence (p = 0.02), with 43% lower odds of right-sided adenoma recurrence in the highest (*vs*. lowest) quartiles of intake (Table IV*b*). Likewise, there was an inverse association between averaged dietary intake of beta-carotene and multiple adenoma recurrence, with 49% lower odds in the highest (*vs*. lowest) quartiles of intake. A similar inverse association appeared

TABLE IIIA – ODDS RATIOS (OR'S) AND 95% CONFIDENCE INTERVALS (95% CI) FOR ANY, MULTIPLE, RIGHT SIDED ADENOMA RECURRENCE BY QUARTILES OF BASELINE SERUM CAROTENOID CONCENTRATIONS: PPT[1]

Median for each quartile ug/dl	OR (95% CI) for any adenoma recurrence	OR (95% CI) for multiple adenoma recurrence	OR (95% CI) for right sided adenoma recurrence
Adenoma/no recurrence	323/511	147/511	217/511
Alpha-carotene			
3	1.00	1.00	1.00
4	0.86 (0.58–1.27)	0.80 (0.49–1.35)	0.85 (0.55–1.33)
7	0.74 (0.49–1.11)	0.79 (0.46–1.34)	0.75 (0.46–1.25)
12	0.66 (0.43–1.02)	0.55 (0.30–0.99)	0.60 (0.37–0.95)
Trend	0.06	0.06	0.03
Beta-carotene			
9	1.00	1.00	1.00
15	1.12 (0.74–1.69)	0.93 (0.54–1.63)	1.28 (0.80–2.03)
24	1.10 (0.73–1.64)	1.29 (0.77–2.18)	1.17 (0.73–1.87)
44	0.84 (0.56–1.28)	0.65 (0.37–1.17)	0.81 (0.50–1.32)
Trend	0.27	0.15	0.18
Beta-cryptoxanthin			
5	1.00	1.00	1.00
8	0.74 (0.49–1.12)	0.56 (0.32–0.96)	0.73 (0.46–1.17)
12	0.89 (0.60–1.34)	0.71 (0.42–1.20)	0.83 (0.52–1.32)
17	0.99 (0.67–1.48)	0.69 (0.40–1.18)	0.90 (0.57–1.43)
Trend	0.72	0.34	0.87
Lutein/Zeaxanthin			
14	1.00	1.00	1.00
20	0.95 (0.62–1.44)	0.85 (0.50–1.46)	1.01 (0.63–1.63)
26	0.92 (0.62–1.36)	0.87 (0.50–1.50)	0.81 (0.51–1.27)
38	0.88 (0.58–1.32)	0.87 (0.50–1.49)	0.86 (0.54–1.37)
Trend	0.52	0.68	0.43
Lycopene			
12	1.00	1.00	1.00
19	1.13 (0.75–1.71)	1.42 (0.83–2.42)	1.12 (0.69–1.80)
26	1.30 (0.87–1.95)	1.17 (0.68–2.03)	1.45 (0.92–2.29)
36	1.22 (0.81–1.86)	1.31 (0.75–2.30)	1.25 (0.78–2.03)
trend	0.29	0.49	0.26
Total Carotenoids			
53	1.00	1.00	1.00
75	0.98 (0.65–1.46)	1.13 (0.67–1.91)	0.97 (0.62–1.54)
97	0.87 (0.58–1.30)	0.89 (0.52–1.52)	0.82 (0.52–1.30)
136	0.77 (0.51–1.16)	0.67 (0.38–1.18)	0.71 (0.44–1.14)
trend	0.16	0.17	0.12
Vitamin A			
49	1.00	1.00	1.00
59	1.40 (0.91–2.14)	1.24 (0.69–2.22)	1.64 (1.01–2.68)
67	1.38 (0.91–2.09)	1.81 (1.02–3.20)	1.57 (0.96–2.57)
81	1.14 (0.74–1.75)	1.32 (0.74–2.35)	1.18 (0.72–1.93)
trend	0.74	0.28	0.80

[1]Models adjusted for age, NSAIDS use, gender, intervention group, gender* group interaction.

between total dietary carotenoid intake and any recurrence, with 40% lower odds in the highest (*vs*. lowest) quartiles. Vitamin A intake from food alone or with supplements was inversely associated with all adverse endpoints. Compared to the lowest quartile of intake of vitamin A from food, the third and fourth quartiles had 52 and 55% lower odds of multiple adenoma recurrence, respectively. Significantly lower odds of any and of right-sided recurrence appeared in the highest compared to the lowest quartiles of intake of total vitamin A. In a comparison by treatment group, a consistent inverse association of averaged dietary intakes of vitamin A (from foods alone as well as supplements) and the OR of adverse endpoints was observed in the intervention, not the control group, but the test for interaction was not significant. Multiple logistic regression models of any and of multiple adenoma recurrence were repeated for males and females separately (data not shown). No significant associations were observed in the gender-stratified analyses nor were the associations significant for the interaction terms (gender*carotenoid or gender*vitamin A).

In an analysis of the percent contribution of each FFQ line item to dietary alpha-carotene intake (averaged over 3 time points), 80% of dietary alpha carotene was accounted for by 3 line items: "carrots or mixed vegetables containing carrots," (65%), "vegetable soups" (8%) and "tomatoes and tomato juice" (7%). (In a linear regression analysis of the predictors of average serum alpha-carotene concentration, only 3 line items in the FFQ were significantly associated with serum alpha-carotene "carrots or mixed vegetables containing carrots," ($p=0.001$), "tomatoes and tomato juice" ($p=.02$) and "cole slaw, cabbage, or sauerkraut" (since cole-slaw contains a small amount of carrots) ($p=0.03$).

DISCUSSION

In the PPT subcohort, baseline serum alpha-carotene concentrations were inversely related to the odds of right-sided adenoma recurrence and dietary intakes of alpha-carotene were inversely related to the odds of any recurrence. The inverse associations of vitamin A intake from food alone and food with supplements and the OR of all adverse endpoints were the most consistent baseline effects observed, along with the significant lower odds in the third and fourth quartiles of intake. All lower odds of recurrence attributed to diet or serum levels at baseline were observed in the intervention not the control group; however the test for interaction was not significant. Significant lower odds of recurrence associated with baseline dietary intakes of alpha-carotene and vitamin A reflect potential long-term habitual intake of foods rich in vitamin A and alpha-carotene, such as carrots. Carrots and mixed vegetables with carrots were the major food contributors to dietary and

TABLE IIIB – ODDS RATIOS[1] (OR'S) AND 95% CONFIDENCE INTERVALS (95% CI) FOR ANY, MULTIPLE, RIGHT SIDED ADENOMA RECURRENCE BY QUARTILES OF BASELINE DIETARY CAROTENOID INTAKE: PPT[1]

Median for each quartile mg/day	OR (95% CI) for any adenoma recurrence	OR (95% CI) for multiple adenoma recurrence	OR (95% CI) for right sided adenoma recurrence
Adenoma/no recurrence	323/511	147/511	217/511
Alpha-carotene			
0.15	1.00	1.00	1.00
0.28	1.12 (0.75–1.69)	1.22 (0.70–2.09)	1.54 (0.96–2.46)
0.42	0.91 (0.60–1.38)	0.81 (0.46–1.42)	1.07 (0.66–1.73)
0.78	0.69 (0.45–1.06)	0.71 (0.40–1.27)	0.83 (0.50–1.37)
trend	0.03	0.11	0.06
Beta-carotene			
1.19	1.00	1.00	1.00
1.96	0.90 (0.60–1.36)	0.97 (0.56–1.67)	1.00 (0.62–1.60)
2.94	0.84 (0.56–1.27)	0.81 (0.46–1.42)	0.98 (0.61–1.58)
4.74	0.75 (0.49–1.15)	0.80 (0.46–1.42)	0.89 (0.55–1.45)
trend	0.18	0.38	0.61
Beta-cryptoxanthin			
0.01	1.00	1.00	1.00
0.02	0.84 (0.56–1.28)	0.58 (0.33–1.03)	0.75 (0.47–1.20)
0.04	1.21 (0.81–1.83)	0.74 (0.43–1.28)	0.83 (0.52–1.33)
0.08	1.00 (0.66–1.52)	0.79 (0.46–1.36)	0.85 (0.53–1.36)
trend	0.71	0.85)	0.79
Lutein/Zeaxanthin			
0.87	1.00	1.00	1.00
1.61	1.11 (0.73–1.67)	0.73 (0.42–1.29)	1.16 (0.72–1.87)
2.48	1.21 (0.80–1.84)	1.00 (0.58–1.71)	1.20 (0.75–1.93)
4.44	0.92 (0.60–1.42)	0.78 (0.45–1.38)	1.02 (0.62–1.67)
trend	0.56	0.63	0.90
Lycopene			
0.95	1.00	1.00	1.00
1.69	1.02 (0.68–1.53)	1.05 (0.60–1.82)	1.14 (0.71–1.81)
2.66	0.83 (0.55–1.26)	0.94 (0.54–1.65)	0.92 (0.57–1.48)
4.27	0.85 (0.56–1.29)	0.95 (0.54–1.68)	0.87 (0.54–1.41)
trend	0.33	0.78	0.37
Total Carotenoids			
3.93	1.00	1.00	1.00
6.06	0.87 (0.58–1.31)	0.80 (0.46–1.39)	0.92 (0.58–1.47)
8.23	0.93 (0.61–1.40)	1.01 (0.58–1.74)	0.93 (0.58–1.49)
13.75	0.71 (0.46–1.09)	0.70 (0.39–1.24)	0.78 (0.48–1.27)
trend	0.14	0.31	0.33
Vitamin A Food			
0.77	1.00	1.00	1.00
1.12	0.76 (0.50–1.15)	0.59 (0.34–1.01)	0.65 (0.41–1.05)
1.53	0.50 (0.32–0.78)	0.33 (0.18–0.59)	0.49 (0.30–0.81)
2.19	0.52 (0.33–0.83)	0.35 (0.19–0.66)	0.46 (0.27–0.78)
trend	0.004	0.001	0.006
Vitamin A Total			
9.90	1.00	1.00	1.00
1.59	0.94 (0.62–1.41)	0.76 (0.44–1.30)	0.98 (0.61–1.56)
2.36	0.73 (0.48–1.11)	0.52 (0.30–0.93)	0.78 (0.48–1.27)
3.52	0.58 (0.37–0.90)	0.48 (0.26–0.87)	0.55 (0.33–0.92)
Trend	0.007	0.011	0.01

[1]Models adjusted for age, NSAIDS use, gender, intervention group, gender*group interaction.

serum alpha-carotene levels. Just as recent observational epidemiologic research has documented that chronic long-term intake of fiber is associated with lower odds of incident polyps, so perhaps long-term intake of vitamin A rich sources and carrots may lower the odds of polyp recurrence.[22]

In the analysis of averaged carotenoids and vitamin A from annual visits in the first 3 years of the PPT, serum concentrations of alpha-carotene and beta-carotene were associated with lower odds of right-sided and of multiple adenoma recurrences. Dietary analyses mirrored the serum findings with dietary intakes of alpha-carotene associated with lower odds of every adverse endpoint. Similar to our baseline findings, dietary intakes of vitamin A were consistently and strongly associated with lower odds of every adverse endpoint. The decreased risk from increasing intake of vitamin A was far more consistent and stronger than for alpha-carotene. Dietary intake of vitamin A is the sum of provitamin A carotenoids and pure vitamin A sources in food; thus the dietary results may perhaps be partially reflected in the patterns observed in serum alpha-carotene and beta-carotene concentrations. Without serum isomers of vitamin A such as retinoic acid or tissue concentrations of metabolites, we cannot explore the underlying molecular pathways from dietary intake of vitamin A to lower odds of recurrence because serum retinol concentrations are under homeostatic control.

Our analysis of the PPT subcohort is the first reported investigation of the association between individual serum and dietary carotenoids as well as vitamin A and adenomatous polyp recurrence in a large prospective study. The protection from adenoma recurrence in PPT participants who had average serum carotenoid concentrations in the highest compared to lowest quartile is consistent with the recent report of a large beta-carotene supplementation adenoma recurrence trial, which employed a similar cohort design. In the latter trial, the relative risk of recurrence among subjects taking beta-carotene supplements who did not drink or smoke was 0.56 (0.35–0.89), while the RR in participants taking beta-carotene supplements who both smoked and drank alcohol was 2.07 (1.39–3.08)7. The beta-carotene supplemented group in 2 large lung cancer trials of smokers (ATBC and CARET) expe-

TABLE IVA – ODDS RATIOS (OR'S) AND 95% CONFIDENCE INTERVALS (95% CI) FOR ANY, MULTIPLE, RIGHT SIDED ADENOMA RECURRENCE BY QUARTILES OF T1–T3[2] AVERAGED SERUM CAROTENOID CONCENTRATIONS: PPT[1]

Median for each quartile	OR (95% CI) for any adenoma recurrence	OR (95% CI) for multiple adenoma recurrence	OR (95% CI) for right sided adenoma recurrence
Adenoma/no recurrence	300/481	135/481	202/481
Alpha-carotene			
2.6	1.00	1.00	1.00
4.7	1.06 (0.69–1.61)	1.12 (0.65–1.92)	1.05 (0.67–1.67)
6.8	0.97 (0.64–1.47)	0.95 (0.53–1.68)	0.95 (0.59–1.55)
12.0	0.70 (0.46–1.09)	0.64 (0.34–1.20)	0.62 (0.37–1.04)
trend	0.07	0.10	0.04
Beta-carotene			
9.8	1.00	1.00	1.00
17.7	0.84 (0.55–1.28)	0.56 (0.32–1.00)	0.79 (0.49–1.27)
28.3	1.06 (0.70–1.62)	1.07 (0.62–1.82)	0.95 (0.59–1.54)
52.0	0.73 (0.47–1.13)	0.40 (0.22–0.75)	0.75 (0.46–1.23)
trend	0.22	0.02	0.37
Beta-cryptoxanthin			
5.7	1.00	1.00	1.00
8.7	0.95 (0.62–1.44)	0.99 (0.56–1.75)	0.99 (0.61–1.61)
12.3	0.88 (0.58–1.34)	0.72 (0.40–1.30)	0.87 (0.54–1.40)
19.7	0.98 (0.64–1.49)	0.88 (0.49–1.55)	0.89 (0.55–1.44)
trend	0.93)	0.54	0.57
Lutein/Zeaxanthin			
15.3	1.00	1.00	1.00
22.3	0.71 (0.46–1.08)	0.60 (0.34–1.06)	0.71 (0.44–1.16)
29	0.63 (0.41–0.96)	0.68 (0.39–1.18)	0.65 (0.40–1.06)
39.3	0.85 (0.56–1.29)	0.70 (0.40–1.20)	0.81 (0.50–1.29)
trend	0.49	0.28	0.41
Lycopene			
12.7	1.00	1.00	1.00
20.0	1.37 (0.90–2.07)	1.45 (0.85–2.49)	1.33 (0.82–2.13)
26.0	1.05 (0.68–1.62)	0.88 (0.50–1.57)	1.16 (0.72–1.89)
34.3	1.04 (0.67–1.62)	0.91 (0.50–1.65)	1.05 (0.63–1.74)
Trend	0.83	0.46	0.98
Total Carotenoids			
58.5	1.00	1.00	1.00
80.3	0.87 (0.57–1.32)	0.78 (0.45–1.35)	0.85 (0.53–1.37)
104.5	0.99 (0.65–1.50)	0.95 (0.56–1.64)	0.92 (0.57–1.48)
145.7	0.76 (0.50–1.16)	0.52 (0.29–0.95)	0.68 (0.42–1.12)
trend	0.27	0.06	0.16
Vitamin A			
50.7	1.00	1.00	1.00
60.7	1.08 (0.70–1.67)	1.04 (0.57–1.91)	0.92 (0.56–1.52)
69.3	1.25 (0.81–1.93)	1.54 (0.85–2.78)	1.35 (0.83–2.18)
81.7	0.92 (0.60–1.42)	1.25 (0.69–2.26)	0.85 (0.52–1.39)
trend	0.75	0.31	0.77

[1]Models adjusted for age, NSAIDS use, gender, intervention group, gender* group interaction.– [2]Average of year 1–3 of study or more than one year of study.

rienced a statistically significant increased risk of lung but not colorectal cancers.[23–25] Further analysis of ATBC and CARET trials demonstrated that participants in the beta-carotene supplemented arm who were also in the highest compared to the lowest quartile of alcohol intake experienced the greatest risk of lung cancer.[26,27] One could argue that the beta-carotene supplementation effects on adenoma recurrence[7] and the serum carotenoid associations observed in the PPT do not relate to colorectal cancer prevention. However, in both trials, the protective effects were observed in more severe forms of adenomas, *e.g.*, advanced adenoma in the beta-carotene supplementation trial,[7] and multiple adenomas (which are associated with a higher probability of cancer than single adenomas)[11,12] in the PPT. Most importantly, our finding of a protective effect of serum carotenoids on adenomatous polyp recurrence adds to the growing body of literature demonstrating protective effects of carotenoids on precursor lesions for colorectal cancer in individuals who do not smoke or drink alcoholic beverages.

Few studies have examined the relation of serum carotenoids or vitamin A concentrations and adenomatous polyps. In a U.S. case-control study using sigmoidoscopy examination, the ORs for adenomas in the highest quartiles of serum alpha-carotene and beta-cryptoxanthin compared to the lowest quartiles were 0.68 (95%CI = 0.48–0.98), and 0.67 (95%CI = 0.47–0.95), respectively, after adjustment for age and gender; further adjustment for fruit and vegetable intakes that are highly correlated with serum carotenoid levels attenuated these associations.[28] In a small study (n=59) in Hungary, lower serum levels of zeaxanthin and vitamin A were observed in colorectal adenoma patients compared to controls.[29] In another study of serum beta-carotene and vitamin A levels, the highest compared to the lowest quartiles of serum vitamin A had significantly reduced odds of colorectal adenoma but no association for beta-carotene.[30] Compared to higher levels of lycopene, lower levels $<$ 70 mg/L were associated with increased odds of incident adenomas.[31] No association of specific serum carotenoid levels to colorectal adenomas has been reported in cohort studies. The relation of serum carotenoids or vitamin A to colorectal cancer risk has been examined in case-control and cohort studies, but no statistically significant associations were reported.[32–39] None of these studies examined serum alpha-carotene concentrations in their analyses.

Few studies have examined the association between dietary carotenoids and adenomas, with inconsistent findings in early studies of colorectal adenomas based on older dietary estimates of total provitamin A carotene, beta-carotene and/or retinol intakes.[40–42] Moreover, no effect on adenoma recurrence was ob-

TABLE IVB – ODDS RATIOS (OR'S) AND 95% CONFIDENCE INTERVALS (95% CI) FOR ANY, MULTIPLE, RIGHT SIDED ADENOMA RECURRENCE BY QUARTILES OF AVERAGED T1–T3[2] DIETARY CAROTENOID INTAKE: PPT[1]

Median for each quartile	OR (95% CI) for any adenoma recurrence	OR (95% CI) for multiple adenoma recurrence	OR (95% CI) for right sided adenoma recurrence
Adenoma/no recurrence	311/484	139/484	209/484
Alpha-carotene			
0.22	1.00	1.00	1.00
0.39	1.23 (0.80–1.87)	0.97 (0.55–1.71)	1.22 (0.75–1.97)
0.58	1.02 (0.66–1.57)	0.90 (0.51–1.60)	1.09 (0.66–1.78)
0.93	0.67 (0.42–1.06)	0.56 (0.29–1.06)	0.57 (0.33–0.99)
trend	0.03	0.05	0.02
Beta-carotene			
1.62	1.00	1.00	1.00
2.89	1.06 (0.69–1.63)	0.91 (0.51–1.61)	1.30 (0.80–2.12)
4.14	0.99 (0.64–1.55)	0.78 (0.43–1.41)	1.00 (0.60–1.66)
6.28	0.68 (0.42–1.10)	0.51 (0.26–1.00)	0.68 (0.38–1.19)
Trend	0.07	0.03	0.06
Beta-cryptoxanthin			
0.02	1.00	1.00	1.00
0.03	1.13 (0.74–1.74)	0.85 (0.47–1.53)	0.86 (0.52–1.40)
0.06	1.49 (0.96–2.30)	0.96 (0.53–1.74)	1.11 (0.67–1.81)
0.11	1.28 (0.81–2.00)	1.00 (0.54–1.83)	0.95 (0.57–1.59)
trend	0.31	0.81	0.90
Lutein/Zeaxanthin			
1.13	1.00	1.00	1.00
2.40	0.88 (0.58–1.35)	0.61 (0.34–1.09)	0.98 (0.61–1.58)
3.71	0.94 (0.61–1.46)	0.93 (0.53–1.640	1.03 (0.63–1.69)
5.90	0.72 (0.45–1.15)	0.65 (0.34–1.23)	0.74 (0.43–1.28)
trend	0.20	0.40	0.27
Lycopene			
1.26	1.00	1.00	1.00
2.20	0.75 (0.49–1.14)	0.83 (0.47–1.47)	0.74 (0.46–1.21)
3.15	0.86 (0.56–1.32)	1.06 (0.60–1.87)	0.84 (0.52–1.38)
5.00	0.67 (0.43–1.03)	0.61 (0.33–1.12)	0.72 (0.44–1.19)
trend	0.12	0.14	0.30
Total Carotenoids			
5.10	1.00	1.00	1.00
8.42	0.92 (0.60–1.40)	0.80 (0.46–1.41)	1.22 (0.76–1.97)
11.64	0.90 (0.58–1.39)	0.74 (0.41–1.34)	0.91 (0.55–1.51)
17.38	0.60 (0.37–0.97)	0.55 (0.29–1.06)	0.70 (0.40–1.22)
trend	0.03	0.08	0.10
Vitamin A Food			
0.92	1.00	1.00	1.00
1.35	0.87 (0.57–1.33)	0.57 (0.32–1.01)	0.90 (0.55–1.46)
1.81	0.68 (0.44–1.07)	0.48 (0.26–0.88)	0.70 (0.42–1.17)
2.48	0.62 (0.38–1.01)	0.45 (0.24–0.86)	0.60 (0.34–1.04)
Trend	0.04	0.03	0.05
Vitamin A Total			
1.34	1.00	1.00	1.00
2.12	0.96 (0.63–1.47)	0.85 (0.48–1.51)	1.12 (0.69–1.83)
2.90	0.92 (0.59–1.43)	0.81 (0.45–1.45)	1.04 (0.63–1.72)
4.28	0.58 (0.36–0.94)	0.53 (0.28–1.00)	0.49 (0.28–0.86)
Trend	0.02	0.05	0.004

[1]Models adjusted for age, NSAIDS use, gender, intervention group, gender* group interaction.– [2]Average of years 1–3 of study or more than one year of study.

served in the only other study to estimate individual dietary carotenoids.[43] Research on the association between dietary carotenoids and colorectal cancer are more numerous, but protective effects have appeared in case-control not cohort studies. The 2 cohort studies to examine dietary carotenoids and colorectal cancer found no associations.[44,45] Two Italian[46,47] and 1 Russian case-control study[48] showed a protective effect of beta-carotene intake on the odds of colorectal cancer. In 2 colorectal cancer case-control studies that examined the major individual dietary carotenoids, a protective association of dietary lutien/zeaxanthin, alpha-carotene, and beta-carotene was observed in a Swiss study,[49] and only dietary lutein/zeaxanthin intake was associated with a significant protective effect that was strongest in the proximal colon in a U.S. study.[50] The finding of protection of carotenoids in the proximal colon is consistent with our lower odds ratios for alpha-carotene in the right colon. Numerous studies have suggested differences in the epidemiology of the proximal and distal colon;[13,14] however, little is known about the concentration of carotenoids in the colonic epithelium.[51] Dietary intakes of vitamin A from food alone or from the addition of supplements have not been associated with risk of colorectal cancers.[52] Overall, findings from prior research did not demonstrate a consistent association between dietary carotenoid and vitamin A intake and risk of adenoma recurrence or colorectal cancer.

Our results support a growing body of evidence showing a protective association between serum or dietary alpha-carotene and cancers of various organ sites, often similar to or in the absence of a significant association between beta-carotene and the disease.[5,53–57] While alpha- and beta-carotene are very similar in structure, 2 animal studies have shown they have different chemopreventive potential. The administration of alpha-carotene, lycopene and lutein, but not beta-carotene, substantially inhibited aberrant crypt foci formation in Sprague-Dawley rats.[58] Also, alpha-carotene was more effective than beta-carotene at inhibiting chemically induced skin tumors, induced lung tumors and spontaneous liver tumors.[59]

Alpha-carotene may not be the sole active agent but a marker for other dietary components, dietary compliance or lifestyle characteristics that are protective against adenoma recurrence. Carrots are a member of the apiaceous vegetables, which have been shown to reduce *CYP1A2* activity in humans, an enzyme that metabolizes various procarcinogens.[60] Recently, serum concentrations of alpha-carotene were correlated with a healthy diet index,[61] suggesting that serum concentrations of alpha-carotene may be a marker for an overall better quality of diet or individuals who are more willing to comply with dietary intervention plans. Since carrots are the major source of alpha-carotene and beta-carotene, and may often be consumed in mixed dishes with other vegetables, it is possible that alpha-carotene is a marker for other protective dietary factors in the same foods or foods consumed concomitantly. While the PPT intervention group increased their consumption of fruits and vegetables, the major increases were from low-carotenoid sources, with 33% of the increase from legumes, apples, potatoes and bananas and only 3% from carrots.[62] The intent of the dietary intervention in the PPT was not to enhance carotenoid intake but to increase overall fruit and vegetable intake, increase dietary fiber and decrease fat. The finding of the reduced adenoma recurrence with higher serum carotenoids *vs*. the null finding for recurrence due to the dietary intervention in the main PPT may reflect the substantially greater exposure differences in the observational (first through fourth quartiles) compared to the experimental (intervention *vs*. control group) analyses.

The strengths of this study include the prospective design, the use of multiple measures of serum concentrations and dietary intake of carotenoids and a large sample size. By averaging serum concentrations and dietary intake over 3 time points rather than using 1 measurement, intraindividual variation in exposure is attenuated, resulting in a more precise estimate of effect. One limitation of our study, however, is that the volunteers for the PPT are relatively healthy nonsmokers, thereby limiting the generalizability of the findings to similar populations. Note the recent study of the beneficial effects of beta-carotene supplements on adenoma recurrence in healthy nonsmoking, nonalcohol drinking populations like the PPT, but the adverse effects in smokers and drinkers.[7] In addition, whereas multiple comparisons increase the possibility of the findings being due to chance, the consistency of effect for vitamin A and for alpha-carotene across different outcomes (any adenoma, multiple adenoma and proximal adenoma), and over time evokes more confidence in the findings. As is well appreciated in the literature, all self-report dietary instruments are subject to measurement error, both random and systematic.[63] Since participants in the intervention group knew exactly what was required of them, their potential misreporting of true dietary intake of fat, fiber, fruit and vegetables, as well as vitamin A and carotenoid rich foods during the 3 years of the intervention, cannot explain the strong baseline effect maintained over the trial period.

This is the first prospective study to report the association between serum and dietary levels of carotenoids and vitamin A and recurrence of any and multiple adenomas, as well as right-sided adenomas in a prospective design. The findings need to be replicated in other prospective studies of adenoma recurrence.

APPENDIX

The members of the Polyp Prevention Study Group participated in the conduct of the Polyp Prevention Trial. However, the data presented in this manuscript and the conclusions drawn from them are solely the responsibility of the above listed co-authors.

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